



# Contrast enhanced ultrasound: comparing a novel modality to MRI to assess for bowel disease in pediatric Crohn's patients

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**Background:** To demonstrate the feasibility and reliability of a novel imaging modality, contrast enhanced ultrasound (CEUS), in evaluating for distal small bowel inflammation in pediatric Crohn's disease (CD), and compare this to concurrently obtained magnetic resonance imaging (MRI) findings.

**Methods:** Pediatric patients diagnosed with or having suspicion of CD with small bowel involvement, whose disease merited imaging with an MRI, concurrently underwent imaging with CEUS. We assessed the ability of CEUS to demonstrate distal small bowel disease by evaluating wall thickness, enhancement pattern, mucosal disruption and pericolonic inflammation. Concordance between imaging modalities was then assessed.

**Results:** Twenty patients were recruited for the study, 16 with known CD, 3 with concern for CD, and one with known colitis, but unknown bowel disease status. Six patients (3 with prior diagnosis of CD, 3 without) had absence of bowel enhancement on both ultrasound and MRI. Eleven patients with findings of inflammation and enhancement on MRI also had concurrent evidence of enhancement on CEUS. Three patients who had no evidence of inflammation on MRI, with known CD, had prominent bowel enhancement on CEUS. One patient with known colitis, whom we enrolled to evaluate for small bowel disease, had no evidence on either MRI or CEUS, however CEUS showed significant fat stranding around the colon, supporting the diagnosis of CD.

**Conclusions:** The sensitivity of CEUS to detect bowel inflammation when seen on MRI was 100%. In addition, CEUS may also have the ability to detect bowel inflammation, even in the presence of a normal MRI.

**Keywords:** Contrast enhanced ultrasound (CEUS); contrast ultrasound; pediatric Crohn's disease (pediatric CD); inflammatory bowel disease; imaging

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## Introduction

The prevalence of Crohn's disease (CD) is highest in North America, with 145–199 cases per 100,000 people (1). It often results in focal, asymmetrical, and transmural bowel inflammation. Assessing for bowel wall involvement and extent of disease is critical, as it can portend the severity

of illness. There is no literature comparing magnetic resonance imaging (MRI) and contrast enhanced ultrasound (CEUS) to qualitatively assess for bowel disease in children. A small study in 2015 assessed 28 children (mean age 14 years) with greyscale ultrasound, who were known to have bowel wall inflammation on MRI. Greyscale ultrasound was found to have a sensitivity of 55% and

specificity of 57% (2). In the adult literature, a study performed in February 2017 compared the presence of bowel disease on MRI versus CEUS in adult patients with severe CD and found a strong correlation between inflammation between the two modalities ( $P < 0.001$ ) (3). Our study aimed to explore a novel imaging technique and corroborate its validity to assess for distal small bowel disease in pediatric patients, thereby providing an alternative imaging modality.

In the past decade, MRI has come to revolutionize diagnostic algorithms in diagnosis and management of CD as it allows visualization of mural thickening, fibrosis, perianal disease and abscesses without radiation as well as subtle secondary signs of bowel inflammation, including pericolonic fat stranding. Despite the advantages of MRI examinations, limitations include the use of oral contrast agents for colonic luminal distension, which can be challenging for children, high cost of MRI, length of the procedure and anesthesia in small children. In comparison, a high quality abdominal ultrasound can assess for bowel wall thickness, vascularization, abdominal free fluid, mesenteric lymph nodes, stenosis, fistulas, and abscesses, without the need for oral contrast or anesthesia (4). Although ultrasound has a lower tissue contrast than MRI, it has a higher spatial resolution which allows for detailed visualization of different layers of the bowel wall. When emphasized with microbubble contrast, which consists of proteins, lipids, and biopolymers that rapidly distribute in the vessels, there may be the potential to accentuate visualization of the bowel wall, and assess for the presence of mucosal disruption, pericolonic fat, and intramural small abscesses, all of which can be a sign of more severe active disease (5). This enhancement of the bowel wall is important as studies have shown that mural thickness of the combined mucosa and submucosa greater than 3 mm, when it is able to be visualized on ultrasound, has a sensitivity and specificity of 88% and 95% respectively for CD and active inflammation (6,7). Thus, this may be the most reliable indicator of small bowel disease. In addition, early neovascularization of the bowel wall, a pathological change seen in CD, is enhanced by microbubbles, and therefore can accentuate areas of early inflammation.

Our goal therefore is to demonstrate both the feasibility and reliability of this novel radiographic technique to evaluate for distal small bowel disease in CD as compared to MRI.

## Methods

### Inclusion

All patients with diagnosed or suspected diagnosis of CD, less than 21 years of age, who merited imaging with MRI based on physician criteria as below, to assess for distal small bowel disease.

### Exclusion

None. If coordinating a same day CEUS delayed patient care in anyway, then patients were not included in the study, and priority was given to obtaining an MRI.

Data, including age, gender, inpatient/outpatient status, reason for obtaining imaging, and ultimate diagnosis were obtained. Congruency of enhancement pattern between MRI and CEUS was recorded for each patient.

After assessment by a board-certified pediatric gastroenterologist at Lucile Packard Children's Hospital Stanford, inpatient and outpatient pediatric patients who had clinical suspicion or diagnosis of CD, based on clinical criteria of abdominal pain, weight loss, bloody stools, fevers, diarrhea, or surveillance needs, who merited further imaging with a contrast based MRI (T1- and T2-weighted images) underwent a CEUS, ideally on the same day. Trained sonographers in conjunction with a board-certified pediatric radiologist at Lucile Packard Children's Hospital with 15 years of experience, performed and interpreted the CEUS. The patients were initially scanned in grayscale to identify the region of bowel wall thickening or inflammation. The bowel was evaluated on grayscale images for signs of inflammation. Inflammation was noted when there was thickening of the mucosa or submucosa, loss of normal bowel stratification, disruption of the muscularis propria, presence of intramural abscesses, increased and hyperechoic fat. If inflammation was not apparent, images of the terminal ileum were obtained. After the area of interest was localized, contrast (sulfur hexafluoride lipid-A microspheres, Lumason<sup>®</sup>, Bracco) was injected at a dose of 0.03 mL/kg. Ultrasound was performed with Philips, GE and Siemens machines, with probes ranging from 6–18 MHz. Degrees of enhancement of the bowel wall and inflammatory fat was assessed over a period of 5 minutes post contrast injection.

We then compared this with findings of inflammation as seen on standard MRI (3T Discovery 750, GE Healthcare,

**Table 1** Patient recruitment table. Inpatient/outpatient status, gender, established prior diagnosis of Crohn's disease, and reason for obtaining imaging

Patient	Age (years)	Location	Gender	Previous diagnosis of Crohn's (Y/N)	Presenting symptoms
1	10	Outpatient	F	Yes, based on biopsies	Abdominal pain, bloody diarrhea
2	9	Outpatient	M	Yes, based on prior imaging	Anal fissures, abdominal pain
3	10	Outpatient	F	No	Weight loss, abdominal pain
4	17	Outpatient	F	No	Abdominal pain, weight loss, nausea
5	18	Inpatient	M	Yes, based on biopsies	Chronic diarrhea, weight loss
6	16	Inpatient	F	No	Abdominal pain, weight loss
7	16	Inpatient	F	Yes, based on biopsies	Anemia, abdominal pain
8	13	Outpatient	F	Yes, based on biopsies	Failure to thrive, anemia
9	17	Outpatient	M	Yes, based on biopsies	Abdominal pain, surveillance given history of abscesses
10	15	Outpatient	M	Yes, based on biopsies	Diarrhea, abdominal pain
11	14	Outpatient	F	Yes, based on biopsies	Bloody diarrhea, abdominal pain
12	15	Inpatient	M	Yes, based on biopsies	Abdominal pain
13	13	Inpatient	F	Yes, based on prior imaging	Anemia, bloody stools
14	17	Outpatient	M	Yes, based on biopsies	Fatigue, weight loss
15	16	Outpatient	M	Yes, based on prior imaging	Abdominal pain
16	13	Outpatient	M	Yes, based on prior biopsies	Failure to thrive, bloody stool
17	16	Outpatient	M	Yes, based on prior biopsies	Bloody stool, fatigue, abdominal pain
18	10	Outpatient	M	Yes, based on prior biopsies	Abdominal pain
19	11	Inpatient	M	Yes, based on prior biopsies	Bloody stools, fatigue, abdominal pain
20	17	Inpatient	F	Known colitis on imaging, unknown small bowel disease status	Abdominal pain, hematochezia

T1- and T2-weighted images with and without contrast), which was read by a different radiologist to avoid bias. MRI was performed in patients after they were asked to drink biphasic oral contrast, which presents as hypointense on T1-weighted images and hyperintense on T2-weighted sequences. The sequences for our examination included a coronal single shot T2-weighted sequence (SSFSE), cinematic thick slab coronal balanced gradient echo to evaluate peristalsis (Coronal FIESTA Dynamic), multiphase coronal T1-weighted fat suppressed images with contrast injection, and axial T2-weighted fat suppressed sequence of the abdomen and pelvis (FIESTA). Disease features on MRI indicative of enhancement included increased wall thickness, high T2 signal intensity and bowel wall transmural hyper-enhancement. We also were able to assess for pericolonic inflammation, which on MRI presents as an

ill-defined region of T2 hyperintense signal and iso-intense T1 signal in the fat surrounding a bowel loop, and mucosal disruption, which is the loss of stratification between continuous areas of bowel wall. The CEUS in most cases were done on the same day as the MRI, however given occasional difficulties of scheduling patients on the same day, or time restraints on behalf of patients, two patients had up to a week discrepancy between the two studies.

## Results

Over the time period from April 2018 to January 2019 we enrolled a total of 20 patients for this study. These patients had an average age of age of 14.2 years of age, with 9 females and 11 males recruited (*Table 1*). Eighty-five percent of patients (n=17) had concordance of bowel

**Table 2** Radiographic findings (CEUS and MRI)

Patient	Contrast enhanced ultrasound (CEUS)			Magnetic resonance imaging (MRI)				Enhancement concordance
	Mucosal disruption	Enhancement	Bowel wall thickness (mucosa, submucosa) in mm	Mucosal disruption	Enhancement	Bowel wall thickness (mucosa, submucosa) in mm	Pericolonic inflammation	
1	No	No	N/A	No	No	N/A	No	Yes
2	No	No	(1.7, 1.1)	No	No	(2.2, -)	No	Yes
3	No	No*	N/A	No	No	N/A	No	Yes
4	No	No*	N/A	No	No	N/A	No	Yes
5	No	No	N/A	No	No	N/A	No	Yes
6	No	No	N/A	No	No	N/A	No	Yes
7	Yes	Yes	(6.7, 4.2)	No	Yes	(6.9, 3.4)	Yes	Yes
8	Yes	Yes	(3, 1.6)	No	Yes	(4.6, 2.7)	Yes	Yes
9	Yes	Yes	(7.7, 2.1)	Yes	Yes	(8.9, 2.8)	Yes	Yes
10	No	Yes	(3, 1.6)	No	Yes	(4, 4.3)	Yes	Yes
11	Yes	Yes	(6.5, 2)	No	Yes	(9.6, 5.6)	Yes	Yes
12	Yes	Yes	(7.2, 4.2)	Unable to determine	Yes	(11.5, 3.9)**	Yes	Yes
13	No	Yes	(2.6, -)	No	Yes	(2, -)	Yes	Yes
14	Yes	Yes	(4.5, 2.5)	No	Yes	(6.2, -)	No	Yes
15	Yes	Yes	(4.3, 2)	Yes	Yes	(-, -)	Yes	Yes
16	No	Yes	(6, 2.7)	Yes	Yes	(8.6, 4.4)	Yes	Yes
17	Yes	Yes	(6.6, 3.6)	No	No	(2.4, -)	Yes	No
18	Yes	Yes	(5.7, 2.9)	No	Yes	(6.3, 3.3)	Yes	No
19	No	Yes	(3.5, 2.2)	No	No	(3.5, -)	Yes	No
20	Yes	No	(7.1, 5.1)	No	No	(12.1, 3.2)	Yes	Yes

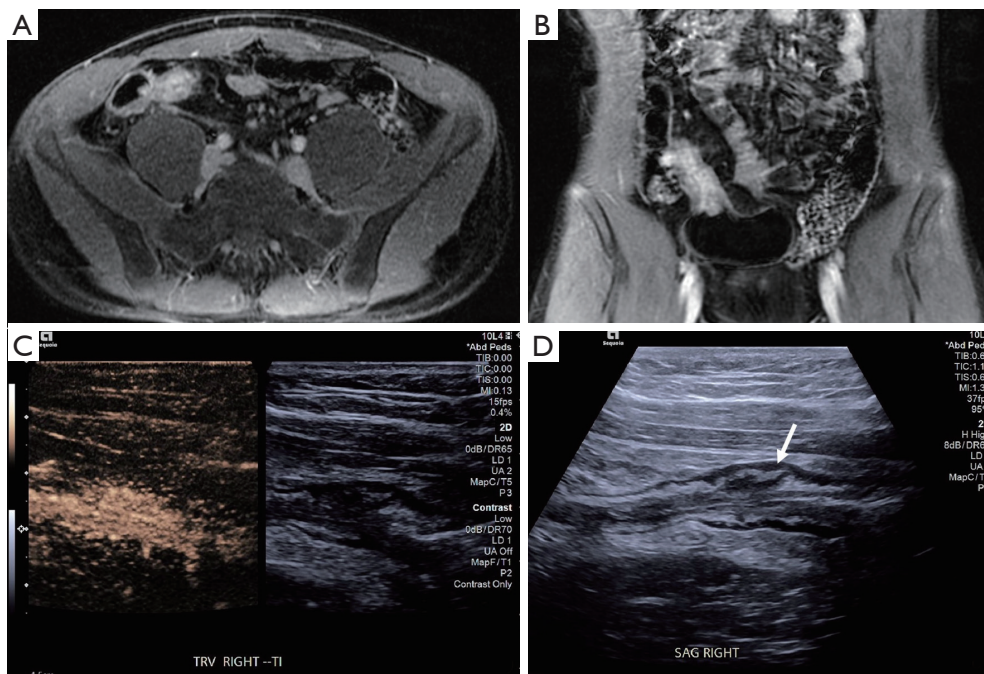
Overall analysis of radiographic findings in recruited patients, noting findings of mucosal disruption, small bowel enhancement, and thickness on both CEUS and MRI. Evidence of pericolonic inflammation on MRI, and concordance of findings between imaging modalities, also noted. \*, no contrast; \*\*, CT study. CEUS, contrast enhanced ultrasound; MRI, magnetic resonance imaging.

enhancement, 6 without enhancement on either modality, and 11 with enhancement on both modalities (*Table 2*). The remaining 3 patients had discordant findings, with inflammations seen on CEUS but not on MRI. Excluding our patients without enhancement on either modality (#1–6), of the remaining 14 patients, all with known CD, 71% (n=10) of patients had signs of mucosal disruption on CEUS, whereas only 21% (n=3) had signs of mucosal disruption on MRI. Radiological evidence of inflammatory fat stranding, a characteristic seen namely in CD, was observed in 93% of patients (n=13).

Six patients (#1–6) recruited in the study, three with

a known diagnosis of CD, had both normal MRI and ultrasound imaging studies. However, two of these patients had traditional greyscale imaging without contrast, given the greyscale was overwhelmingly normal in appearance. Eleven patients who had a known diagnosis of CD, with previously known small bowel disease, had findings of small bowel disease on both CEUS and MRI (*Figure 1*). One of these patients had a CT done in lieu of an MRI.

There were three patients with known CD who had normal MRI studies without significant enhancement; however, all three had prominent enhancing bowel loops on CEUS (Cases #17–19). Although patient #18 had very



**Figure 1** A 17-year-old boy with known Crohn's disease based on biopsy, MRE T1-weighted fat suppressed post contrast images in (A) axial and (B) coronal planes show marked transmural terminal ileal thickening and enhancement. (C) CEUS shows concordant marked enhancement, transmural wall thickening and mucosal disruption. Of note, (D) greyscale US using a 10 L linear probe on this Siemens machine allows high resolution visualization of bowel wall layers, even an intramural abscess (arrow). CEUS, contrast enhanced ultrasound; MRE, magnetic resonance enterography.

subtle enhancement on MRI, there was very prominent enhancement on the CEUS, and in essence this could be viewed as discordant (*Figure 2*). Patient #20 in this study had an unknown diagnosis of CD, with colitis on biopsy, and underwent both a magnetic resonance enterography (MRE) and CEUS, both revealing colonic disease without small bowel enhancement; however the CEUS noted significant pericolonic fat stranding around the colon, not previously noted on MRI.

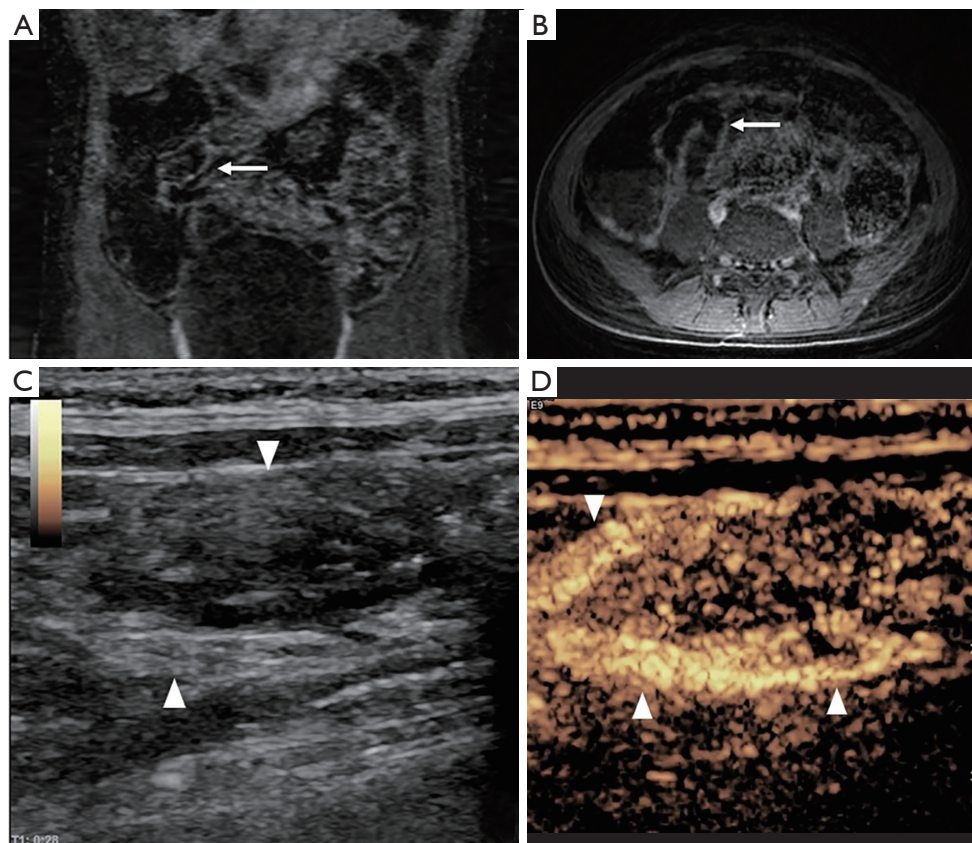
## Discussion

In our study, we demonstrate the feasibility and reliability of CEUS for CD in children. All the patients who had findings of small bowel inflammation on cross sectional studies (MRI in 11 patients and one patient on CT) had evidence inflammation on CEUS, making the sensitivity of our study 100%. Two patients in this study had findings of enhancement on CEUS which was not seen MRI; and one patient although had showed enhancement of the small bowel on both studies, the level of enhancement on CEUS

was markedly more pronounced compared to the subtle findings on MRI. One patient had known colitis and was undergoing imaging to evaluate for small bowel disease to distinguish between UC and CD, and had only colonic involvement on both modalities. However, this patient did have notable inflammatory fat around the colon on CEUS, giving supportive evidence for CD. Although this was not our specific intention, pericolonic fat is mainly seen in CD, and not in ulcerative colitis, and helped to make a salient diagnosis for this patient. Due to the high resolution of ultrasound, subtle changes in mucosal and submucosal thickening could be detected on ultrasound while not visible on MRI.

In terms of the overall ability to highlight areas of inflammation in general, CEUS was able to show enhancement of the submucosa and mucosa of the bowel in all 14 of our patients with CD, and pick up signs of mucosal disruption in nearly 71% of these patients. Obviously, the ability to evaluate these objective findings is dependent on the bowel segment that is visualized, but given we were able to see a depth of enhanced bowel greater than 3 mm





**Figure 2** A 10-year-old boy presenting with abdominal pain, normal examination on MRE (A,B) with minimal enhancement noted in distal ileal loops (arrow). However, (C) greyscale and corresponding (D) CEUS performed the same day showed brisk intense enhancement with wall thickening of a distal ileal loop of bowel (arrowheads). Biopsy confirmed Crohn's disease. CEUS, contrast enhanced ultrasound; MRE, magnetic resonance enterography.

(indicative of inflammation) in all of our patients, this was very reassuring, especially given that our controls had no enhancement to any degree.

From a safety standpoint, CEUS has a proven track record. Thirty-four subjects ranging in age from 8 months to 20.7 years underwent 134 CEUS procedures with no significant side effects, and all tolerated the procedure well (8). An additional study examined the records of 305 pediatric patients aged 1 month to 18 years, who were undergoing CEUS for a variety of etiologies, including renal, vascular, trauma, and liver concerns, and none had adverse reactions related to CEUS (9). Some of these patients also had MRI studies done synchronously with their CEUS, similar to our study design, and none had any adverse outcomes. Our IRB has also reviewed the safety merits of microbubble contrast, in conjunction with MRI contrast, and deemed there was no excessive burden of risk

placed patients, and we had their written approval prior to enrolling patients.

The discretion of enrollment was completely up to the patient, and if some caregivers did not want to participate, they were excluded, which may have biased our patient selection. Furthermore, we only consented patients who had an MRI ordered by their provider, and given that providers have different thresholds and reasons for ordering MRI studies, this could also have biased on our population sample. Given that we wanted to demonstrate findings, and prove the feasibility of this study in a relatively short time frame, we did not perform this study on patients if we felt there was a strong suspicion of functional abdominal pain, and therefore we enrolled patients who would likely have small bowel inflammation.

We realize that though we could quantify the degree of inflammation on CEUS, we were not able to quantify the

extent of bowel disease on CEUS, given that ultrasound has a small field of view compared to MRI, which is one of the major limitations of ultrasounds. Therefore, due to a lack of a reliable quantitative, post-processing tool to evaluate quantitatively for degree of bowel enhancement, we sought to obtain namely qualitative as opposed to quantitative data for the purposes of our study. We are also aware that CEUS can evaluate additional radiological findings such as fat stranding (as noted in one patient), abscesses, strictures, fistulas, etc.; however given the enrollment size of our initial group, we were not able to evaluate these in further depth, but this can be a consideration in future studies.

In addition, given our radiological ultrasounds machines and contrast software was constantly upgraded, we used machines from three different vendors, and therefore the different machines may have subtle differences in their abilities to assess for enhancement. Furthermore, given ultrasound is limited in some degree by the technician and by the limited field of view; unlike the case of an MRI, we may not have been able to visualize a particular loop of bowel of interest due to the smaller field of view.

An additional consideration is that for the purposes of this study, we assumed that the MRI was the gold standard of inflammation, wherein all practically, the gold standard would be actual small bowel biopsies. Although nearly all patients had prior evidence of small bowel inflammation histologically, many of these had these biopsies chronologically separated from our study (i.e., biopsy several years ago for diagnosis of CD) and therefore we could not corroborate either MRI or CEUS with a true gold standard of current and real-time small bowel inflammation. Furthermore, in the cases where CEUS showed inflammation but MRI was normal, we had no gold standard to corroborate this was not a false positive result. We also aimed to have as many studies done temporally within 24 hours of each other, but due to scheduling and patient time constraints two patients may have had up to a week delay between the MRI and CEUS, and theoretically they could have had a change in disease burden, either for better or worse, during this time, which may have biased our results.

Despite the limitations of the study, in conclusion, we illustrated that CEUS can accurately detect and assess for small bowel inflammation, particularly in patients with CD. Feasibility of CEUS would help in reducing the limitations of performing MRE in pediatric patients; mainly necessity of oral contrast, time of exam, cost and possibility of sedation. However, more structured, controlled, and larger

population sizes would be required to truly potentiate this imaging modality as a valid and recognizable modality. Overall, there may be a significant role for using CEUS in assessing for pediatric small bowel inflammation in CD.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ethical Approval: Stanford IRB Approval 42949. Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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